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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,802	12/17/1999	Mariano A. Garcia-Blanco	1579-321	9348

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/465,802	Applicant(s) Garcia Blanco
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *June 20, 2003 and August 15, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *5-10* is/are pending in the application.

4a) Of the above, claim(s) *6-10* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *20*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. In view of the newly received Supplementary Amendment, the previous Final Rejection is vacated.

1. The Amendment filed June 20, 2003 (Paper No. 16) in response to the Office Action of December 20, 2002 (Paper No. 15) is acknowledged and has been entered. New Claims 6-8 have been added and have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. The Supplementary Amendment filed August 15, 2003 (Paper No. 19) is acknowledged and has been entered. New Claims 9-10 have been added and have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claim 5 is currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant has previously canceled claims 1-4 and added claim 5 (drawn to the subject matter of canceled claims 1-4), a method of determining the likelihood of metastasis of a prostate tumor in a human patient comprising assaying said tumor for FGF-R2 IIIc isoform mRNA wherein expression of the FGF-R2 isoform mRNA indicates said tumor is likely to metastasize for examination. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claims 6-8 directed to methods of (1) assessing androgen sensitivity of a prostate tumor comprising assaying for FGF-R2 IIIc isoform, (2) determining the likelihood of metastasis of a prostate tumor comprising assaying for FGF-R2 IIIb isoform mRNA, (3) assessing androgen sensitivity of a prostate tumor

comprising assaying for FGF-R2 IIIb isoform mRNA, have been withdrawn from consideration as being directed to a non-elected inventions, the embodiments of claims 9-10 directed to method of (4) assaying the androgen sensitivity of a prostate tumor in a human patient and (5) a method of determining the likelihood of metastasis of a prostate tumor in a human patient comprising assaying said tumor for FGF-R2 IIIb isoform mRNA wherein loss of expression of the FGF-R2 isoform mRNA indicates said tumor is likely to metastasize have been withdrawn from consideration as being directed to non-elected inventions and only a method of determining the likelihood of metastasis of a prostate tumor in a human patient comprising assaying said tumor for FGF-R2 IIIc isoform mRNA wherein expression of the FGF-R2 isoform mRNA indicates said tumor is likely to metastasize will be examined . See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03. Newly submitted claims 6-10 are directed to inventions that are independent or distinct from the invention originally claimed because the inventions of claim 5 and the inventions of claims 6-10 are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

4. The following objections are maintained:

5. Objection to the specification drawn to the status of the parent application is maintained. Applicant requests clarification of the requirement to reflect status of the parent application. Although the parent application is a provisional application, the status of all parent applications is required. The status of the parent is "now abandoned". The specification must be amended to reflect the status of the parent application.

6. The following rejections are maintained:

Claim Rejections - 35 USC § 112

7. Claim 5 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No.15, Section 9, pages 3-11.

Applicant argues in Paper No. 16 that (a) the enablement of the claims is not based solely on *in vitro* Dunning Model cultured cells. Example 1 describes the identification of a cis-acting element in rat FGF R2 that is required for proper slicing regulation of the IIIc exon which causes repression of the IIIc exon, effects exclusive to DT3 cells (a well differentiated androgen-dependent rat prostate cancer line) and Example 1 provides an extensive description as to how to practice the claimed methods, (b) Carstens et al, 1997, incorporated by reference, show that in both the androgen independent cell lines and the androgen independent xenograft, androgen insensitivity was correlated with loss of the FGF-R2 (IIIb) isoform, (c) Examiner's comments regarding the Carstens et al article are noted, however the comments overlook the fact that the authors state, in this peer-reviewed article, that their results show a correlation between loss of IIIb isoform of FGF-R2 and androgen insensitivity in human prostate tumors and the finding that in PC-3 cells the FGF-R2 gene appears either to be not expressed or somehow has been lost in no way negates this fundamental finding, (d) Applicant points to the introduction of the Carstens article and the introduction of the Yan et al article, both of record and states that Examiner is reminded that androgen-insensitivity is correlated with metastatic potential of human prostate tumors. In view of this accepted correlation, no basis is seen for Examiner's

suggestion that the Carstens et al data are not relevant to metastatic potential of human prostate tumors.

The arguments have been considered but have not been found persuasive because (a') Although the techniques described in Example 1 are well known in the art, Example 1 is drawn to *in vitro* studies and for the reasons previously set forth, these studies do not provide enablement for the claimed invention, (b') as previously set forth, the Carstens reference is not commensurate in scope with the claimed invention and in the absence of objective evidence demonstrating the suitability of these models for extrapolation to the human *in vivo* condition, it would not be expected that any of these models would be suitable for determining the likelihood of metastasis. It is noted that Applicant has not submitted objective evidence of the suitability of these models, (c') although the reference concludes that the results using the models can be correlated to androgen insensitivity in human prostate tumors, the models used are not suitable for the reasons of record. Further, the authors state, also on p. 3063, left column, that the observations made using the Dunning rat prostate cancer model point to loss of FGF-R2 (IIIb) as being an important event in the development of androgen insensitivity and that similar findings in human prostate cancer have not been previously described. It is noted that the authors do not state that the loss of the IIIb isoform is either a necessary or sufficient event for the development of androgen insensitivity. Since the invention is drawn to an undeveloped art the evidence presented is not sufficient to enable the claimed invention, (d') A review of the introduction to the Carstens et al reference reveals that the authors state that elucidation of the biological processes which cause prostate cancer to both metastasize

and develop androgen independent growth is needed (col 1). The reference further states that it is proposed that growth factors are key elements which mediate the effects of androgens on prostate cell growth and differention and that disruption of this system (FGF family) may (emphasis added) be a step which is involved in tumor development and progression (col 2). The reference does not make any statement regarding a correlation between androgen insensitivity and metastatic potential. In fact, it appears that the authors separate the processes of metastasis and androgen independent growth. Although a review of the Yan et al introduction reveals that there is a shift from relatively slow growing nonmetastatic androgen-sensitive tumors to a rapidly growing androgen-independent, highly malignant state in prostate cancer, the reference does not make any statement regarding a correlation between androgen insensitivity and metastatic potential. The reference specifically states that a lack of knowledge of mechanisms underlying the appearance of the malignant tumors has hampered design of strategies for prediction and prevention of their appearance (col 1) and for the reasons of record, the Carstens et al data is not relevant to metastatic potential of human prostate tumors.

Applicant argues in Paper No. 19 that (a) Drexler et al, Zellner et al and Embleton et al relate to tumor types other than prostate tumor and thus are irrelevant to the present invention, (b') it is not contended that the FGF-R2 IIIc isoform is the "cause" of a prostate tumor becoming metastatic, rather that this alternative splicing provides a marker useful in determining the likelihood of metastasis.

The arguments have been considered but have not been found persuasive because (a') neither the cited references nor the exemplification discussed are drawn to

tumor types, but rather are drawn to cell lines, all of which those of ordinary skill in the art recognize are subject to the artifacts of the in vitro system. The references were cited to demonstrate the artifactural natural of cell lines. It is noted that Applicant does not argue that cell lines do not develop artifacts or that the information from cell lines can be directed extrapolated to the *in vivo* condition, (b') since neither the specification nor the art of record teach that this "marker" is either necessary or sufficient for determining the likelihood of metastasis it is not clear how, based only on the information in the specification, how one can use this "marker" to distinguish tumors that are likely to metastasize from those that are unlikely to do, especially in view of the teachings of US patent No. 5,830,640, of record.

Finally, it is noted that Applicant does not address the teachings of US Patent No. 5,830,640 of record, the teachings of Van Weerden, of record, the teaching of Hill, of record, drawn to relevance of models to metastatic human tumors and the question of whether expression of the IIIc isoform is a rate limiting step for determining the likelihood of metastasis.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

8. No claims allowed.

9. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO

MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 18, 2003